Alternative Mechanisms for the Interaction of the Cell-Penetrating Peptides Penetratin and the TAT Peptide with Lipid Bilayers

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Supporting Material

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Supplementary Material

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Methods

General setup

The simulations of the isolated peptides in water were performed in a truncated tetrahedral box whereas all other simulations were performed in a rectangular box. The temperature was maintained by coupling the peptides, lipids and water to separate heat baths at 320 K using the Berendsen weak coupling method (1) with a time constant of 0.1 ps. The pressure was maintained at 1 atm again using the Berendsen weak coupling approach (1). The pressure coupling was isotropic for the simulations of peptides in water and semi-isotropic for the simulations involving membranes. A time constant of 10 ps was used for the equilibration of the pure membranes while a time constant of 1 ps was used for all other simulations. The masses of all hydrogen atoms in the peptide and lipid were increased to 4 a.u. with the masses of the heavy atoms to which they are attached decreased accordingly (2). This allowed a time step of 4 fs to be used for integrating Newton's equations of motion. While the redistribution of the masses alters the local dynamics of specific groups it does not affect the thermodynamic properties of the system significantly. Note, the force field combination used is well-tested and has been used previously to successfully simulate a number of peptide-membrane systems (3, 4)

Umbrella integration technique

The umbrella integration technique proposed by Kästner and Thiel (5) reconstructs the free energy profile by numerical integration of the average net force acting on the peptide after correcting for the effect of the restraining potential in each window. Umbrella integration has the advantage over other methods such as the weighted histogram (WHAM) approach (6) in that it is not iterative and is less dependent on the degree of overlap between the windows. The average net force in each window was computed numerically from the mean and the variance of the coordinates within each

window. A Fortran 90 implementation of the umbrella integration technique compatible with Gromacs 3.3.x and Gromacs 4.0.x is available on request.

Table 1. Summary of the simulations performed.

Simulation		Lipid type and number	Peptide type and number	Counter ions	Length ns.	Number of windows	Interval along Z, nm
Peptides in water		–	Penetratin, 1	Yes	25		
		–	TAT, 1	Yes	25		
Pure bilayers		DPPC, 128	–	No	50		
		DOPC, 128	–	No	50		
TAT binding to small bilayer		DOPC, 128	TAT, 4	Yes	200		
		DOPC, 128	TAT, 4	No	200		
Pepide binding to large bilayer		DPPC, 512	Penetratin, 8	Yes	50		
		DPPC, 512	TAT, 8	Yes	50		
Pulling	Forward	DPPC, 128	Penetratin, 1	Yes	~100		
		DPPC, 128	TAT, 1	Yes	~100		
	Reverse	DPPC, 128	Penetratin, 1	Yes	~50		
Umbrella sampling	Structures from forward pulling	DPPC, 128	Penetratin, 1	Yes	100 per window	67	-0.1; 3.2
		DPPC, 128	Penetratin, 1	Yes	50 per window	9	0.1; 0.5
		DPPC, 128	TAT, 1	Yes	80 per window	71	-0.1; 3.4
	Structures from reverse pulling	DPPC, 128	Penetratin, 1	Yes	20 per window	51	-1.0; 1.5
		DPPC, 128	Penetratin, 1	Yes	50 per window	9	0.1; 0.5

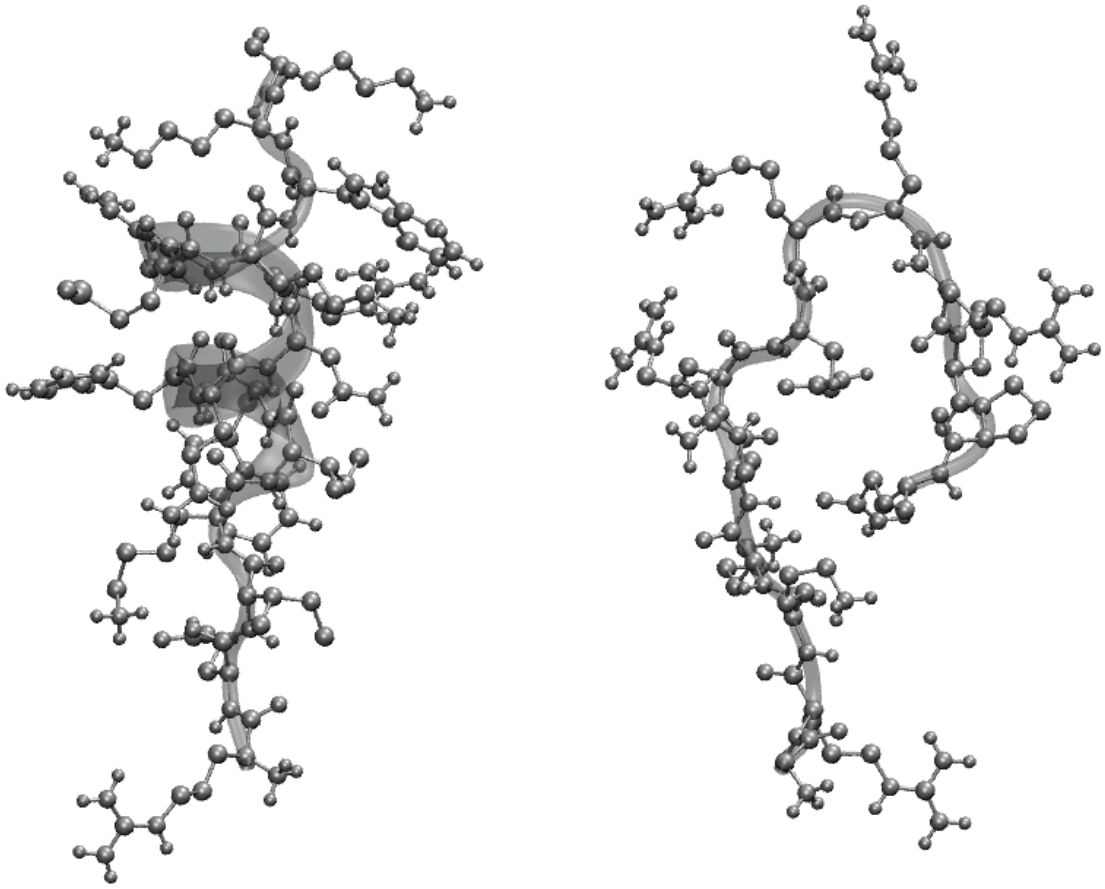

Fig. S1. Structures of the Penetratin (left) and the TAT peptide (right) after 25 ns of simulation in water. The peptides are shown as balls and sticks as well as cartoon representations.

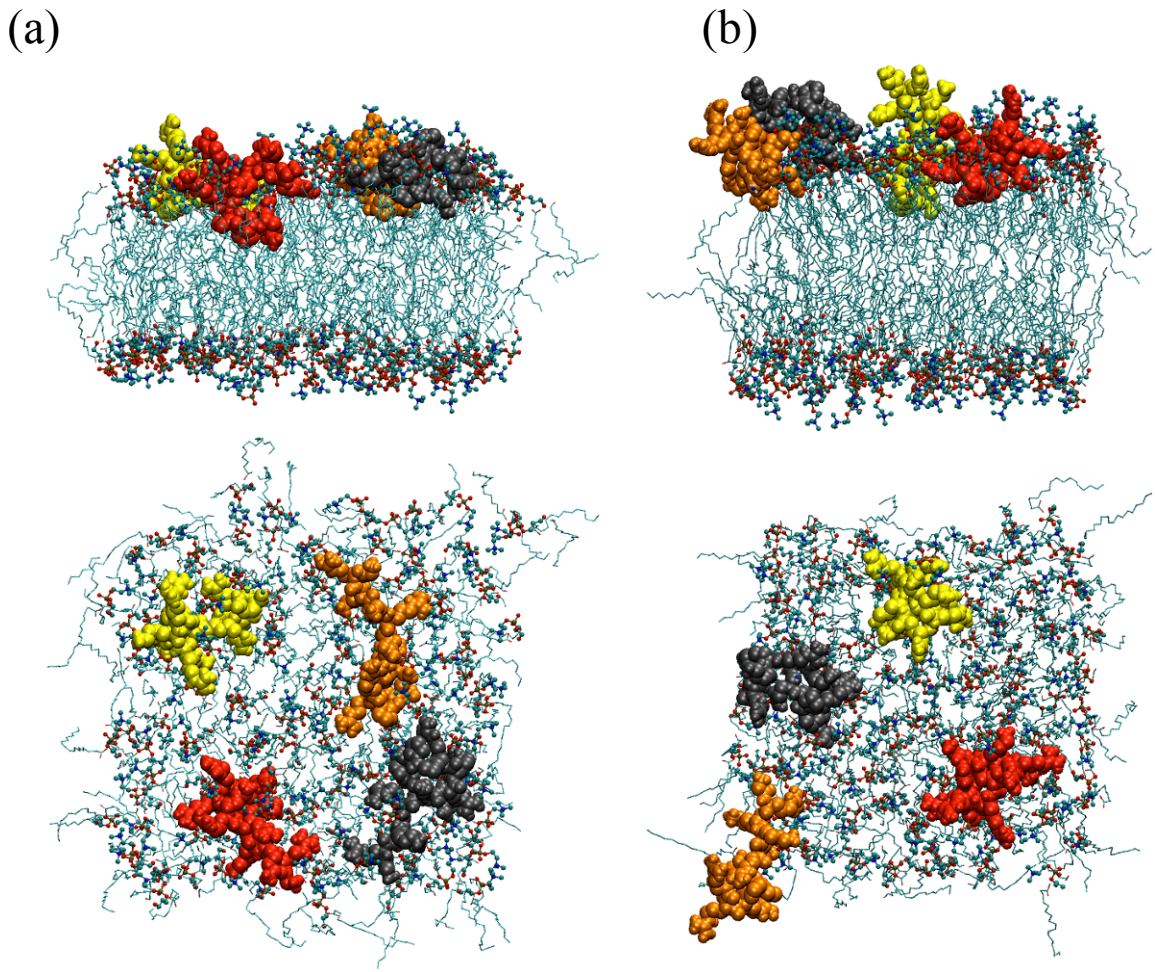

Fig. S2. Snapshots of the DOPC bilayers containing 128 lipids with four bound TAT peptides taken after 200 ns of simulation. Side and top views are shown in the top and bottom rows respectively. The lipid tails are shown as sticks, lipid head group as balls and sticks and the peptides are in the space-fill representation. Each peptide is shown in a different color. a) The system without the counter ions. b) The system with the counter ions. The differences in the surface area and the thickness of bilayer are clearly seen. Water molecules are not shown for clarity.

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